

REMARKS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

Claim 1 was objected to because the term "homologous" was misspelled. In response, Applicants have now corrected the error.

Claims 1, 5, 6, 8-12, 14-24, 26 and 27 were rejected under 35 USC § 112, first paragraph, as being broader than the enabling disclosure. In response, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Applicants have limited the claims to *mice* without prejudice to pursuing broader claims in a divisional application.

At the top of page 7 of the Office Action, the Examiner says the disclosure "does not demonstrate the information required by the Artisan to reasonably make and use *** any short hairpin RNA (shRNA) construct under control of any ubiquitous promoter integrated by homologous recombination at any polymerase II locus." In the next paragraph, the Examiner says the exemplification is limited to Rluc and luciferase. In response, Applicants draw the Examiner's attention to the fact that enablement is not limited to the exemplified embodiments. The examples are meant to be just that—exemplary of the broader disclosure, all of which must be taken into consideration. The fact is that a large number of shRNA sequences were known in the prior art that persons skilled in the art would expect would be operable and a large number of these are expressly set forth in the instant specification, for example, SEQ ID NOS.: 19-220, and, moreover, the specification teaches these work. The fact that Applicants have not

exemplified each and every one of these embodiments does not cast doubt on Applicants' teachings in the specification that these and other embodiments do work. Where, as here, a large number of embodiments would be expected to work, there is no good reason to require Applicants to limit to exemplified embodiments only.

On page 8, the Examiner takes the position that the degree of attenuation and length of time attenuation is achieved is not predictable. Inasmuch as Applicants do not claim in any of the rejected claims any particular degree of attenuation or any length of time in which attenuation is achieved, this position is irrelevant. It is sufficient that Applicants claim a method of gene knock down and have now amended claim 1 to require that the gene knock down be achieved. Since the rejected claims require operability and the Examiner has not made out a case of lack of operability, the alleged unpredictability as to factors not demonstrated by the Examiner to be critical is not a good basis supporting this rejection.

Towards the bottom of the same page, the Examiner says the art teaches stable integration at any polymerase II dependent locus would not necessarily yield predictable gene knockdown. In response, Applicants point out that, as noted above, the rejected claims require that gene knockdown be achieved. Accordingly, the Examiner's comments, which relate to inoperable embodiments that are not claimed, are irrelevant.

On page 9, the Examiner raises another issue in that the rejected claims embrace fish. This is moot since, as noted above, the claims are now limited to mice.

On page 11, the Examiner raises the same issue, this time with respect to claim 27, that the claim embraces fish. Again, Applicants have limited to mice.

In view of the foregoing, Applicants respectfully submit that this rejection is overcome as to the rejected claims. An early notice to that effect is earnestly solicited.

Applicants also respectfully request that special consideration be given to new claims 31-38. Applicants believe these claims do not introduce new matter. Applicants further believe these claims are clearly enabled by the instant specification. An early notice to that effect is also earnestly solicited.

Claims 1, 5, 6, 8-12, 14-24 and 26 were rejected under 35 USC § 112, second paragraph, as being indefinite, allegedly for omitting essential steps. In response, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Applicants point out that the admonition of the second paragraph of section 112 is that the "claims particularly [point] out and distinctly [claim] the subject matter *which the applicant regards* as his invention." The Examiner has not shown Applicants regarded their invention as being limited to integration into ES cells. Consequently, the claims cannot be indefinite for failing to recite such limitation.

With respect to the achievement of a gene knockdown phenotype, Applicants believe this is implicit from the preamble. Nevertheless, in order to advance the prosecution, a positive statement that a gene knockdown phenotype has been achieved has been added to claim 1.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. An early notice that this rejection has been reconsidered and withdrawn is also earnestly solicited.

Claims 1, 5, 6, 8-10, 14-16, 18, 20-24, 26, 27 and 30 were rejected under 35 USC 103(a) as being obvious over McCaffrey et al. ("McCaffrey"), *Nature*, 418: 38 (2002), or Beach et al. ("Beach"), US 2003/0084471, and Bronson et al. ("Bronson"), *Proc. Natl. Acad. Sci. USA*, 93: 9067 (1996). In response, Applicants respectfully submit that the cited combination of references does not make out a *prima facie* case of obviousness. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

In the first paragraph of the rejection, the Examiner says the rejection is to the breadth of the claims as none of the claims require any specific expression level that results in knockdown. In response, Applicants point out that claim 1 has been amended to require that a gene knockdown is, in fact, achieved. This was believed to be implicit by virtue of the preamble, but has now been made explicit. Applicants, therefore, respectfully request that the Examiner reconsider and withdraw this rejection.

Beyond this, Applicants remind the Examiner that cited combinations of references must enable the hypothesized modification to the same extent that the specification of the claimed invention must enable the claimed invention. Where the combinations of cited references do not enable the hypothesized combination, there is no reasonable expectation of success and a *prima facie* case of obviousness is not made out.

See, In re Le Grice, 133 USPQ 365, 374 (CCPA 1962):

“[T]he proper test of a description in a publication as a bar to a patent as the clause is used in section 102(b) requires a determination of whether one skilled in the art to which the invention pertains could take the description of the invention in the printed publication and combine it with his

own knowledge of the particular art and from this combination be put in possession of the invention on which a patent is sought. [Emphasis added.]”

See also, In re Hoeksema, 158 USPQ 596, 601 (CCPA 1968), wherein the Court stated:

“While *In re Le Grice* was bottomed on an issue arising under 35 U.S.C. 102 where the reference was a ‘printed publication,’ that test, in our view, is also properly applicable to issues arising under 35 U.S.C. 103.”

The Examiner concedes at the top of page 16 and towards the middle of page 17 that neither McCaffrey nor Beach discloses stably integrating a shRNA expression construct into a polymerase II dependent locus for any purpose, let alone for achieving gene knockdown. According to the Examiner, Bronson teaches production of transgenic mice by pro nuclear injection of DNA in order to achieve expression of exogenous DNA sequences for many purposes. However, the Examiner concedes that Bronson does not teach expressing shRNA in a specific locus or for the purpose of achieving gene knockdown as a result.

In connection with the lack of enablement rejection, the Examiner has taken the position that it was not predictable that stable integration of shRNA at a polymerase II dependent locus would be successful. See the middle of page 8, for example, where the Examiner finds the "art also teaches stably integrating at any polymerase II dependent locus would not necessarily yield predictable gene knock down." Consequently, the Examiner himself establishes a lack of a reasonable expectation of success that integration of shRNA sequences at a polymerase II dependent locus will result in gene knockdown. The examples in the instant specification show gene knockdown is

successfully achieved and the claims have now been amended to require that gene knockdown is successfully achieved.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw this rejection as well. An early notice that this rejection has also been reconsidered and withdrawn is earnestly solicited.

Claims 1, 5, 27 and 30 were rejected under 35 USC § 103(a) as being obvious over McCaffrey or Beach in view of Bronson in view of Soriano et al. ("Soriano"), US 6,461,864. In response, Applicants point out that this rejection was dependent upon the combination of McCaffrey or Beach in view of Bronson rendering *prima facie* obvious the basic features of the present invention, which has been explained above is not, in fact, the case. The Examiner relies on Soriano to show expression from the rosa26 locus.

However, such expression is still not of a shRNA or for the purpose of achieving gene knockdown. Accordingly, the combination of McCaffrey, Beach, Bronson and Soriano still fails to teach the achievement of gene knockdown by incorporation of shRNA at a polymerase II dependent locus with a reasonable expectation of achieving successful gene knockdown.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw this rejection as well. An early notice that this rejection has also been reconsidered and withdrawn is earnestly solicited.

Claims 11, 12, 17 and 19 were rejected under 35 USC 103(a) as being obvious over McCaffrey or Beach in view of Bronson and Soriano and further in view of Ohkawa et al. ("Ohkawa"), Hum. Gene Ther., 11: 577 (2000). In response, the combination of McCaffrey, Beach, Bronson and Soriano is dealt with above. Ohkawa is cited only to

show inducible promoters, which, therefore, does not overcome the deficiencies in the combination of McCaffrey, Beach, Bronson and Soriano.

In view of the foregoing, Applicants also request that this rejection be reconsidered and withdrawn. An early notice that this rejection also has been reconsidered and withdrawn is earnestly solicited.

Claims 1, 5, 6, 8-12, 14-24, 26, 27 and 30 were provisionally rejected on the ground of obviousness-type double patenting over claims 14-16 and 18-44 of copending Application No. 10/531,347. In response, Applicants respectfully request that this rejection be held in abeyance until allowable subject matter is indicated at which time Applicants will take appropriate action, for example, file a terminal disclaimer or prove patentable distinction.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,
NORRIS McLAUGHLIN & MARCUS, P.A.

By //Kurt G. Briscoe//

Kurt G. Briscoe
Attorney for Applicant(s)
Reg. No. 33,141
875 Third Avenue - 18th Floor
New York, New York 10022
Phone: (212) 808-0700
Fax: (212) 808-0844